



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of : **Confirmation No. 3564**
Sadanobu SHIRAI et al. : Attorney Docket No. 2005_0152A
Serial No. 10/524,858 : Group Art Unit 1615
Filed February 18, 2005 : Examiner Hasan Syed Ahmed
PATCHES
CONTAINING TULOButEROL : **Mail Stop Amendment**

RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

THE COMMISSIONER IS AUTHORIZED
TO CHARGE ANY DEFICIENCY IN THE
FEE FOR THIS PAPER TO DEPOSIT
ACCOUNT NO. 23-0975.

Sir:

Responsive to the Office Action of June 28, 2007, the time for responding thereto being extended for one month in accordance with a Petition for Extension of Time submitted herewith, Applicants submit the following remarks in support of the patentability of the presently claimed invention over the disclosure of the reference relied upon by the Examiner in rejecting the claims. Further and favorable reconsideration is respectfully requested in view of these remarks.

Thus, the rejection of claims 1-3 under 35 U.S.C. §103(a) as being unpatentable over USP 6,117,447 (Nakano et al.) is respectfully traversed.

The Nakano et al. reference is cited in Applicants' IDS of May 18, 2005, and as pointed out in item 6 of the IDS, it corresponds to JP 11-228395 which is also cited in the IDS. The JP '395 reference is cited on page 1 of the present specification, and Comparative example 6 on page 14 of the present specification corresponds to Example 8 of JP '395 (corresponding to the Nakano et al. reference).

As pointed out in the discussion of JP '395 beginning on page 1 of the present specification, when a patch of JP '395 is preserved for a long time, changes in temperature, etc. influence the patch due to the high concentration of tulobuterol. For

example, even if the preparation has good quality just after preparing it, with the passage of time there is a possibility that the drug-release pattern becomes different from the pattern at an earlier time because tulobuterol crystallizes in the adhesive layer or its concentration changes.

The object of the present invention is to provide a patch in which tulobuterol is contained in a lower concentration, but the patch has controllability of stable drug-release.

This object is achieved by the present invention, which provides a patch prepared by laminating an adhesive layer consisting of a rubber, an adhesive resin, a plasticizer, 1 to 4 w/w% of tulobuterol as an active ingredient and 0.1 to 3 w/w% of a higher fatty acid (such as a C₁₁₋₂₂ fatty acid) as a drug release controlling agent on a backing.

In comparing the preparation of the present invention with the preparation disclosed in Nakano et al., they are the same in rubber, adhesive resin, and plasticizer used therein. However the content of tulobuterol contained in an adhesive layer is different from each other, namely the preparation of the present invention relates to one containing a lower concentration of tulobuterol (1 to 4 w/w %), and the preparation disclosed in Nakano et al. relates to one containing a higher concentration of tulobuterol (**not less than 5 wt %**). Furthermore the preparation of the present invention contains a higher fatty acid (such as a C₁₁₋₂₂ fatty acid) as a drug-release controlling agent as an essential component, but the preparation disclosed in Nakano et al. does not contain such a fatty acid, but rather, contains a **fatty acid ester** such as isopropyl myristate as a solubilizer (an additive).

Explaining these differences in more detail, attention is directed to the following descriptions in Nakano et al.:

“These publications mostly relate to a preparation containing tulobuterol in a plaster layer in a concentration of not less than solubility of the drug in an adhesive, wherein tulobuterol is partially dispersed in the plaster layer in a crystalline state”. (Column 1, lines 39-43)

“In view of the above, the present invention now provides a percutaneous absorption type preparation containing tulobuterol dissolved in a plaster layer at a **high concentration of not less than 5 wt %**”. (Column 2, lines 7-10) (Emphasis added)

“Thus, the present invention provides the following. (1) A percutaneous absorption type preparation comprising a support and a plaster layer laminated thereon, said plaster layer comprising tulobuterol in a proportion of not less than 5 wt % in a dissolution state and an adhesive”. (Column 2, lines 11-15)

“(2) The percutaneous absorption type preparation of (1) above, wherein the adhesive is an acrylic adhesive or a rubber adhesive”.
(Column 2, lines 16-18)

[Note: The acrylic adhesive or rubber adhesive is not different from those (rubber, adhesive resin and plasticizer) used in the present invention as indicated by Examiner at page 3 of the Office Action.]

“(8) The percutaneous absorption type preparation of any of (1) to (7) above, wherein the plaster layer further comprises at least **one additive selected from the group consisting of an ester of a fatty acid having 12 to 16 carbon atoms, monoglyceride of a fatty acid having 8 to 10 carbon atoms, an ester of a dibasic acid having 6 to 10 carbon atoms, a polyoxyethylene alkyl ether**, in a proportion of 5 to 50 wt %”. (Column 2, lines 48-59) (Emphasis added)

[Note: The term “C₁₁-C₂₂ fatty acids” indicated by Examiner at page 3 of the Office Action can not be found in the reference.]

“Conventional preparation containing tulobuterol in a dissolution state in a plaster layer could achieve only a concentration of **not more than 3 wt %**, and the present invention is the first to achieve a preparation containing tulobuterol in a dissolution state in a concentration of **not less than 5 wt %, preferably not less than 10 wt %**”. (Column 3, lines 24-30)

“In the present invention, a **solubilizer** can be added to the plaster layer, so that tulobuterol therein has a higher solubility in a plaster layer, and high concentration tulobuterol can be kept in complete dissolution. For example, at least one member selected from an ester of a fatty acid having 12 to 16 carbon atoms, monoglyceride of a fatty acid having 8 to 10 carbon atoms, an ester of dibasic acid having 6 to 10 carbon atoms, a polyoxyethylene alkyl ether, can be used.

Examples of the above-mentioned ester of a fatty acid having 12 to 16 carbon atoms include **C₁ to C₁₀ alkyl esters of C₁₂ to C₁₆ fatty acid**, such as hexyl laurate (C₁₂), isopropyl myristate (C₁₄), isopropyl palmitate (C₁₆) and the like”. (Column 4, line 48 to column 5, line 3).

As a particularly preferred solubilizer (additive) among the additives, **isopropyl myristate** is illustrated (Column 5, lines 29-30).

The kinds of additives, and the amounts of tulobuterol contained in the preparations of each example and comparative example are listed up and summarized in Table 1 (Column 9).

As is also clear from the Table 1, the amount of tulobuterol contained in the preparations is 5 wt %, 10 wt % or 20 wt %, and **no higher fatty acid is used**.

As explained above, the content of tulobuterol disclosed in Nakano et al. is 5 wt % or more; and as another ingredient, a solubilizer or an additive disclosed in Nakano et al., use is made of an ester or ether, etc., and a higher fatty acid (such as a C₁₁₋₂₂ fatty acid) is **not** used or disclosed therein.

As indicated above, the patch of Comparative example 6 of the present specification corresponds to the patch of the Example 8 of Nakano et al. (See page 14, lines 9-10, Japanese Patent Publication A 11-228395 corresponding to Nakano et al).

As shown in Table 1 and Fig. 3 of the present application, the patch of Nakano et al. is far inferior to a patch of the present invention (a patch of Example 1) in drug permeability.

In summary the present invention is clearly different from the preparation disclosed in Nakano et al. in the problem to be solved and the means for solving the problem, as well as even in its effect. A skilled person in the art would not have found it obvious to use a higher fatty acid such as a C₁₁₋₂₂ fatty acid in a patch containing tulobuterol in a lower concentration of 1 to 4 wt %, nor would the art-skilled have found that such a patch would have a superior and stable release controllability. That is, there would have been no motivation to use a C₁₁₋₂₂ fatty acid with the expectation of obtaining the improved patch preparation containing tulobuterol in the lower concentration of 1 to 4 wt %.

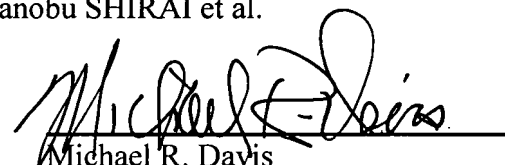
For these reasons, Applicants take the position that the Nakano et al. reference fails to establish a presumption of obviousness of the presently claimed invention. Furthermore, even if the Examiner has established such a presumption, it has been overcome by the showing of unexpected superior results achieved in accordance with the present invention as compared to the reference, as discussed above.

Accordingly, in view of the foregoing remarks, it is submitted that the ground of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

Sadanobu SHIRAI et al.

By:

A handwritten signature in black ink, appearing to read "Michael R. Davis", is written over a horizontal line.

Michael R. Davis

Registration No. 25,134

Attorney for Applicants

MRD/pth
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
October 29, 2007